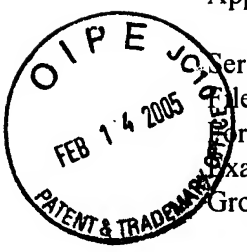
[258] Attorney Docket No. : AGI-131.2US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicant	:	David A. Brown, Alexander A. Khorlin, Krystyna Lesiak and Wu Yun Ren
Serial No.	:	10/667,630
Filed	:	September 22, 2003
For	:	DERMATOLOGICAL COMPOSITIONS AND METHODS
Examiner	:	N. Nutter
Group	:	1711

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with 37 CFR §1.56 and 37 CFR §1.97(c), applicants wish to call the Examiner's attention to References 99-142 listed on the Supplemental Modified 1449 Form submitted herewith. Copies of these references are enclosed.

References 99-101 were cited in a December 23, 2003 communication from the European Patent Office regarding the EP regional phase of PCT Application No. PCT/US97/16642, from which this application claims priority. A copy of the EPO communication, as well as the claims to which it is directed, are attached hereto as Exhibit A. References 99-101 are references D14, D16, and D17 of the communication. The remaining references cited in the communication were previously made of record in this application (see References 2, 4-5, 7, 12, 20, 28, 30-32, 34-35, 38, and 60 of applicants' prior Modified PTO 1449 Form).

Also submitted herewith is a translation of Section 8 of Reference 101 (D17 of the EP prosecution). That section discusses the use of various compounds as choleretics, including two bicyclic monoterpene diols (compounds XIc and XIi of Figure 11).

Commonly-assigned U.S. Patent No. 5,990,177 (Reference 23 of applicants' prior Modified PTO 1449 Form), states that stimulation of the NO/cGMP/PKG pathway is useful for treatment of microvascular irregularities in the liver with consequences for biliary transport and tissue regeneration. The '177 patent cites Suematsu et al., 1996, Cardiovasc. Res., 32:679-686 (Reference 102 of the attached Supplemental Modified PTO 1449 Form), in connection with this disclosure.[1]

[1] References 120-142 submitted herewith are the remaining references which are referred to in the '177 patent in connection with its list of diseases that can be treated through the NO/cGMP/PKG pathway (see column 3, line 12, to column 4, line 5, of the '177 patent).

References 103-119 submitted herewith are the results of a literature search performed to determine if the NO/cGMP/PKG pathway is, in fact, involved in the choleretic activity of the two bicyclic monoterpene diols discussed in Section 8 of Reference 101.

The literature search found that some studies refer to nitric oxide or cGMP dependent mechanisms for choleresis (Myers et al., 1996 (Reference 115); St-Pierre et al., 1996 (Reference 116); Trauner et al., 1997 (Reference 118); Trauner et al., 1998 (Reference 119); and Taniai et al., 2001 (Reference 117)). However, there are many more studies showing choleresis is mediated by a cAMP dependent pathway (Barnhart and Combes, 1975 (Reference 104); Levine and Hall, 1976 (Reference 113); Larsen et al., 1979 (Reference 109); Anwer et al., 1984 (Reference 103); Kaminski and Deshpande, 1984 (Reference 108); Lenzen et al., 1992 (Reference 110); Lenzen and Tavoloni, 1993 (Reference 111); McGill et al., 1994 (Reference 114); Francis et al., 2004 (Reference 107); LeSage et al., 2004 (Reference 112)).

A paper was also found which showed choleresis induced by bombesin independent of cAMP, cGMP or Ca++ (Cho, 1997 (Reference 106)).

In addition, the literature search identified a medicinal compound, i.e., Epomediol (Clesidren)(1,3,3-trimethyl-2-oxabicyclo 2.2.2 ocatan-6,7-endo, endo-diol), which is approved in Italy for use in increasing bile secretion and is a bicyclic monoterpene diol with an oxygen within the bicyclic ring structure. This drug appears to act by stimulating ATPase, Ca++, and adenylate cyclase (Barrera and Parola, 1984 (Reference 105)). No studies were found connecting Epomediol with nitric oxide or cGMP.

Overall, the majority of the papers find that choleresis is induced via a cAMP dependent pathway, not a cGMP process, which means that nitric oxide is not part of the mechanism. Therefore, applicants believe that it would be incorrect to conclude that a compound that induces choleresis acts via the nitric oxide pathway. In particular, applicants submit that it would be incorrect to conclude that the bicyclic monoterpene diols of Reference 101 act via nitric oxide/cGMP to induce choleresis. In addition to the weight of the academic studies, the work on the medicinal compound Epomediol leads to the conclusion that bicyclic monoterpene diols induce choleresis via an adenylate cyclase/cAMP pathway, not the NO/cGMP/PKG pathway of applicants' claims.

Applicants would also like to bring to the attention of the Examiner the following papers of abandoned U.S. Application No. 09/086,548, which was filed on May 28, 1998 in the

names of David A. Brown and Wu Yun Ren: 1) the application as filed, 2) an August 24, 1998 Response to Election of Species Requirement, 3) a September 12, 1998 Office Action, 4) a January 12, 1999 Amendment, and 5) an April 14, 1999 Final Office Action. A copy of these papers is attached hereto as Exhibit B.

The Examiner is respectfully requested to initial a copy of the Supplemental Modified 1449 Form submitted herewith and return it to applicants to indicate consideration of the references listed thereon in connection with the prosecution of this application.

Pursuant to 37 CFR §1.97(c) and 37 CFR §1.17(p), a check for $180.00 is enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment, to Deposit Account No. 11-1158.

Respectfully submitted,

Date: 2/10/05

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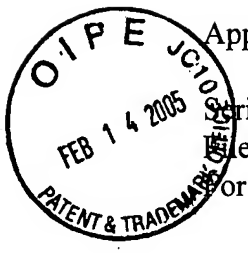

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SUPPLEMENTAL MODIFIED 1449 FORM

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Issue Date	Name
_____	99.	5,190,978	3/1993	Nakamura et al.
_____	100.	5,525,635	6/1996	Moberg

OTHER ART

Examiner Initial

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_____ 104. Barnhart et al., "Characteristics Common to Choleretic Increments of Bile Induced by Theophylline, Glucagon and SQ-20009 in the dog," Proceedings of the Society for Experimental Biology and Medicine, 150:591-596, 1975.

_____ 105. Barrera et al., "Effect of Epomediol on the ATPase and Adenylate Cyclase Activities in Plasmamembranes Isolated from Rat Liver," Pharmacological Research Communications, 16:1133-1140, 1984.

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